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Localization of Endocardial Ectopic Activity by Means of Noninvasive Endocardial Surface Current Density Reconstruction

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Abstract

Localization of the source of cardiac ectopic activity has direct clinical benefits for determining the location of the corresponding ectopic focus. In the present study, a recently developed current-density-based localization approach was experimentally evaluated in noninvasively localizing the origin of the cardiac ectopic activity from body surface potential maps (BSPMs) in a well-controlled experimental setting. The cardiac ectopic activities were induced in 4 well-controlled intact pigs by single-site pacing at various sites within the left ventricle (LV). In each pacing study, the origin of the induced ectopic activity was localized by reconstructing the current density (CD) distribution on the endocardial surface of the LV from the measured BSPMs and compared with the estimated single moving dipole (SMD) solution and precise pacing site (PS). Over the 60 analyzed beats corresponding to ten pacing sites (six for each), the mean and standard deviation of the distance between the locations of maximum CD value and the corresponding PSs were 16.9 mm and 4.6 mm, respectively. In comparison, the averaged distance between the SMD locations and the corresponding PSs was slightly larger (18.4 ± 3.4 mm). The obtained CD distribution of activated sources extended from the stimulus site also showed high consistency with the endocardial potential maps estimated by a minimally invasive endocardial mapping system. The present experimental results suggest that the CD method is able to locate the approximate site of origin of a cardiac ectopic activity, and that the distribution of the current density can portray the propagation of early activation of an ectopic beat.

Keywords

Electrocardiophysiology; body surface potential mapping; electrocardiographic inverse problem; current density reconstruction; single moving dipole; cardiac pacing

1. Introduction

Noninvasive imaging of cardiac electrical activities has been studied for cardiac source localization and identification of abnormal myocardial areas, also potentially for guiding therapeutic treatments of cardiac disorders. It is of importance to better understand the mechanisms of cardiac physiology and pathophysiology and further to develop clinically applicable, noninvasive cardiac mapping techniques. A number of efforts have been put forth in the past decades in the development of the noninvasive cardiac electrical imaging techniques to estimate the equivalent cardiac source inversely from body surface potential

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mappings (BSPMs, Gulrajani *et al* 1984a, Burnes *et al* 2000, He and Wu 1997, 2001, Li and He 2001, Tilg *et al* 2002, Zhang *et al* 2005), magnetocardiographic (MCG, Agren *et al* 1998, Leder *et al* 1998a, Fenicir 2003) field mappings, or directly by comparing the BSPMs (SippensGroenewegen *et al.* 1990, Green *et al.* 1994, Potse *et al.* 2000), body surface Laplacian maps (He & Cohen 1992, 1995, He *et al.* 1993, He & Wu, 1999, Wu *et al.* 1999), or body surface charge maps (He *et al.* 1995) with a data base or known information about cardiac electrophysiology such inverse approaches include equivalent dipole solutions (Ideker *et al* 1977, Savard *et al* 1980, Gulrajani *et al* 1984b, Armoundas *et al* 2003, Lai *et al* 2010), epicardial potential imaging (He and Wu 1997, Burnes and Rudy *et al* 2000), heart surface activation imaging (Huiskamp and Greensite 1997, Dam *et al* 2009, Tilg *et al* 2002), and three-dimensional activation imaging (He and Wu 2001, Li and He 2001, He *et al* 2002, 2003, Zhang *et al* 2005, Liu *et al* 2006, Liu *et al* 2008, Han *et al.* 2008) which depend on different cardiac source models.

Solving the inverse problem of ECG or MCG in terms of endocardial/epicardial surface current density (CD) reconstruction (CDR) has been reported (Leder *et al* 1998a, Muller *et al* 1999) to noninvasively localize cardiac electrical sources. Experimental results in localization of abnormal ventricular activity have been presented, e.g. abnormal atrioventricular pre-excitation sites associated with the Wolff-Parkinson-White (WPW) syndrome (Leder *et al* 2001a), malignant ventricular tachycardia (VT) focus (Muller *et al* 1999) and late potential sources in myocardial infarction (MI) (Leder *et al* 2001b). Similar CDR methods have also been applied in detecting decreased current amplitude in myocardial infarction patients to identify viable myocardial area in the heart (Leder *et al* 1998b, Nenonen *et al* 2001, Goernig *et al* 2009). Although the CDR inverse solutions have been reported promising for the noninvasive estimation of electrophysiological properties of cardiac ectopic activity, most work so far has been focused on qualitative analysis with a few examples. Rigorous *in vivo* experimental validation and statistical evaluation are thus needed to further assess such CDR inverse localization technique before establishing its clinical applicability.

In the present study, our focus was on experimentally evaluating the endocardial surface CDR approach by using an *in vivo* and intact large mammalian animal model (swine), whose cardiac size, heart-torso geometry, and electrophysiological characteristics were chosen to best approximate those of an adult human. An endocardial pacing protocol was used to induce well-controlled ectopic activity where the CDR solutions can be quantitatively evaluated in terms of pacing.

2. Materials and methods

2.1 Principle of current density reconstruction

In the present study, the electrocardiographic (ECG) inverse problem is defined as the problem to reconstruct equivalent current density distributions on the endocardial surface of the left ventricular (LV) from body-surface electrical measurements by applying the minimum norm least square (MNLS) method. The BSPM measurements at a single given time point t obtained from m body surface electrodes can be modeled using a matrix-vector linear model (He 2004):

$$\Phi(t) = \mathbf{L} * \mathbf{J}(t) + \mathbf{N}(t) \quad (1)$$

where $\Phi(t)$ is a $m \times 1$ column vector consisting of m body surface recorded potentials, the $\mathbf{J}(t)$ is a $3n \times 1$ vector consisting of the equivalent current densities at all of the n discrete endocardial surface locations, each of which corresponds to three orthogonal current

sources, $\mathbf{L}$ is the source-to-sensor transfer matrix representing the system transfer coefficients from all $3n$ sources to the locations of m electrodes, and $\mathbf{N}$ is the $m \times 1$ noise vector. By adding the constraint that the sum of the strength of all dipole sources has to be the minimal, the heavily underdetermined equation system (1) can be solved and the MNLS solution equation of CDR can be represented as (He 2004):

$$\min \Delta = \|\Phi(t) - \mathbf{L} * \mathbf{J}(t)\|^2 + \lambda \|\mathbf{WJ}(t)\|^2 \quad (2)$$

where $\|\cdot\|^2$ symbolizes the squared Euclidean norm, $\mathbf{W}$ is a diagonal location weighting matrix $\mathbf{W}$ for depth bias removal and λ is the regularization parameter (Fuchs *et al.* 1999). The MNLS method derived by Wang *et al.* (1992) has been widely used to solve Equation (1), which was also used in this study to provide a unique inverse CDR solution that is the best estimate in the least-squares sense. The current density distribution source model used in this paper is characterized by two properties: 1) the dipole source (at an assigned fixed-location while with arbitrary strength and direction) locations are given in advance over the endocardial surface of the LV, 2) there is always a model term (the second term of the equation (2)) and a regularization parameter λ by which it is linked to the data term (the first term of the equation (2)). Both are necessary because there are so many source locations that the problem would otherwise have no unique solution due to the large number of free parameters (He & Wu, 2001, Compumedics USA Ltd. 2008).

In this study, the current density distribution was calculated for early QRS complex in steps of 1 ms after pacing. For the relatively small time window of around 20 ms after pacing, only the myocardia near the pacing site are depolarized and generate a resultant bioelectric current distribution. Meanwhile, the rest of the heart is still in a resting status where there flows a conduction current, as illustrated in the left panel of Fig. 1. The cardiac electric sources from this small area of depolarized myocardia are assumed to be restricted near the pacing site on the endocardial surface. Therefore, the current density distribution on the endocardial surface of the LV at the early stage of QRS complex could approximate the electrical activity of the whole heart, as illustrated in the right panel of Fig. 1. The endocardial surface of the LV was divided into several hundreds of small patches, and the current density model used for source localization consists of several hundreds of myocardial current dipole sources correspondingly located on these patches. Each of the computed dipoles reflects the cardiac electrical activity of the small patch it represents, thus resulting in a spatially segmented image of the cardiac electrical activity, which relates the calculated current dipole distribution of the heart to the recorded body-surface ECGs for early QRS complex. The CDR method used in this study was minimum norm (Wang *et al.* 1992) and the fitting routine was the method of least squared.

2.2 Swine Model and experimental measurements

The schematic diagram of our experimental evaluation studies is shown in Fig. 2. Experiments were carried out on four control pigs according to a protocol approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Minnesota. The cardiac ectopic activities were induced in each pig by single-site pacing on various sites within the LV. The surgical preparation of these animals for hemodynamic and electrical monitoring has been previously reported (see Fig. 2(a)) (Liu *et al.* 2008). During the pacing studies, each animal was anesthetized with fentanyl infused at 0.75 mcg/kg/min; all were intubated and mechanically ventilated with 65% air and 35% O₂ to maintain a PaCO₂ of 40 ± 2 mmHg. Endocardial surface pacing from LV apex (LVA), LV lateral wall (LVL), LV septum (LVS), or LV anterior (LVAn) sites was accomplished by a quadripolar EP catheter (MarinR, Medtronic Inc., Minneapolis, Minnesota, MN, USA). The 3D locations of the LV pacing sites (PSs) were recorded on the reconstructed LV geometry acquired with a clinical

noncontact mapping (NCM) system (by the Ensight 3000 system, St. Jude Medical Inc., St. Paul, MN, USA).

For each animal, the preoperative magnetic resonance (MR) imaging (MRI; ECG gated to end diastole) was acquired approximately 5-7 days before the *in vivo* pacing experiment so as to obtain the needed anatomical geometry information (see Fig. 2(b)). On the pacing study day, the body surface potential mapping and intracavitary noncontact mapping were simultaneously performed during the pacing protocol. For the body surface potential mapping (see Fig. 2(c) and (f)), 3 fiducial points were located at the precordial, under the left and right armpits separately, and up to 90 disposable electrodes were placed on the anterior and lateral chest (see Fig. 2(a)). The body surface electrodes were referenced to the Wilson central terminal. The 3D locations of the body surface electrodes and the fiducial points were digitized by using an electromagnetic localizer (Fastrak, Polhemus Inc., Colchester, VT, USA).

2.3 Computational solutions and evaluation protocol

In the present study, we employed the boundary element method (BEM) to construct the numerical volume conductor model of heart and torso and solved the corresponding forward problem, which involved the calculation of the potential distribution on the body surface generated by equivalent cardiac sources. For each animal, the realistic three-dimensional (3-D) volume conductor model was constructed individually based on the preoperative MRI scans and prior known physiological knowledge. The MR images were segmented to obtain the detailed boundaries of the heart, the lungs, and the torso (Ramanathan and Rudy 2001), respectively (see Fig. 2 (e)). Piecewise isotropic conductivities of 0.2, 0.04, and 0.6 S/m for the torso, the lungs, and the heart were assumed (Geddes and Baker 1967), respectively. Afterwards, the endocardial surface of the ventricles was segmented carefully (see Fig. 2 (h)); then, the obtained surface of the LV was divided into a number of small patches. Each patch contained an equivalent current source.

Off-line data processing was performed firstly on the recorded BSPM data and the corresponding body surface isopotential maps were obtained (see Fig. 2(f)); then, the CDR inverse problems were solved in the heart-torso volume model by the MNLS method with an automatically optimized regularization λ (Compumedics USA Ltd. 2008) in the CURRY software package (Compumedics, Charlotte, NC, USA). For each pacing study, six well-captured beats were selected for analysis. Those beats were further preprocessed to remove noise and baseline shift. Next, by using the MNLS algorithm, the equivalent cardiac source distribution was inversely reconstructed on the endocardial surface of the LV for the early stage of QRS complex in steps of 1 ms after pacing (between the spike instant of pacing stimulation and the onset instant of the subsequent QRS complex). The spatial resolution of the reconstructed cardiac source distributions was 1 mm. The resultant current density distribution was analyzed and the obtained results in terms of the magnitude of the current density was depicted by means of a color coded surface plot of the LV (see Fig. 2(h)).

Lastly, the accuracy of the inverse solution approach was quantitatively evaluated in terms of the localization errors (LE) of the initiation sites (ISs) of the paced ectopic activity. The

LE statistical analysis included measuring the 3D distances $D_i = (D_{ix}^2 + D_{iy}^2 + D_{iz}^2)^{1/2}$, where x , y , and z are corresponding to the axis X , Y , and Z , respectively) between the pacing sites (PSs) and estimated locations with maximum value of CDR over the selected i ($i=1, 2, 3...6$) beats for each pacing study (Muller *et al* 1999, Bai *et al* 2007). Then, the overall average distance D_m was estimated from the following equation:

$$D_m = \frac{1}{n} \sum_{i=1}^n (D_{ix}^2 + D_{iy}^2 + D_{iz}^2)^{1/2} \quad (3)$$

and the overall standard deviation (SD) was obtained from:

$$S_d = \left(\left(\sum_{i=1}^n (D_i - D_m)^2 \right) / (n - 1) \right)^{1/2} \quad (4)$$

In the present study, each heart was paced at endocardial locations within the LV with an EP catheter. The precise locations of the endocardial pacing sites and the endocardial geometries of the LV were both obtained by the NCM system (see Fig. 2(d)). In order to determine the precise locations of the pacing sites reflected in the resultant heart-torso models, the endocardial surface maps were extracted from the NCM recordings and then registered with the corresponding surface of the beating heart segmented from the preoperative MR images. A rigid image co-registration approach used here for the LV pacing sites was the same as that used in our previous study (Liu *et al* 2008). After the registration, the precise locations of the pacing sites within the LV were determined in the heart-torso model and could be directly compared with the estimated locations of maximum CDR points, and additionally with the optimal sites by means of the single moving dipole (SMD) localization approach. The SMD used to represent cardiac electrical activity is defined as one dipole source, freely movable within the heart, whose resultant body surface potentials would be the closest to the measured one. We have previously evaluated the SMD method in a similar experimental protocol, and suggested that the initial location of the moving dipole can provide the approximate site of origin of a cardiac ectopic activity *in vivo* (Lai et al 2010) (see Fig. 2(h)).

In addition to the comparison of 3D locations among the PSs, the maximum CDR points, and the optimal SMD, distributed information (Bai *et al* 2007), about the extents of the active cardiac areas at the onset of the QRS complex was also estimated which was depicted by means of a color coded surface plot of the LV with a threshold set at 90% of the maximum current density ($\mu\text{A}/\text{mm}^2$) (see Fig. 2(h)). Then, in terms of cardiac electrophysiology, the estimated cardiac electrical distributions were evaluated qualitatively by comparing with the active areas as identified from intracavitary noncontact mappings of the LV, which were displayed by means of a color coded surface plot of the LV with a threshold set at 90% of the maximum potential (mV) (see Fig. 2(d)).

3. Results

Table 1 is a summary of the modeling and experimental parameters. The present study was conducted on four well-controlled pigs. In total, ten endocardial sites within the LV were paced, and 60 paced beats were analyzed (six for each site). The pre-operative MRI data was obtained with a slice thickness of 3 mm and pixel size of 1.7×1.7 mm. The numerical heart-torso volume conductor model and the corresponding endocardial surface model of the LV were constructed for each animal based on their individual pre-operative MR images. Each model consisted of the boundary surfaces of the heart, the lungs and the torso, and contained over 5,000 triangular boundary elements. The number of left ventricular current sources used from the current density calculation was around 700 - 950.

Fig. 3. shows an example of the reconstructed heart-torso volume conductor model and the body surface potential measurements in pig #1. This individual heart-torso model consisted of 5,104 triangular boundary elements including the torso, the lungs and the heart. The endocardial surface of the LV was segmented into 923 patches, each of which would be represented by a corresponding pre-fixed dipole source. The displayed ECGs in a butterfly format were recorded by 88 surface electrodes when the heart is captured by pacing. The locations of the electrodes are shown on the volume conductor model. For the induced activation, both the pacing spike instant and the QRS onset instant are indicated in one of the recorded BSPM signal waveform in Fig. 3. (No. 35 channel, the corresponding electrode of this channel is marked on the volume model). In this study, the early QRS complex of the ectopic beat after pacing was manually defined as three sub-stages for further determining the QRS onset instant, including the artificial spike stage I, the inapparent activation stage II, and the apparent activation stage III, as shown in Fig. 3. Stage I is an artificial spike phase when the time window is usually less than 5 ms after the pacing stimulation and the pacing artifact recorded in BSPMs decreased the signal-noise rate (SNR) in the first 5 ms of activation. Stage II is an inapparent activation phase when the SNR might be either lower or occasionally a little bit higher than that of normal ECGs. In stage II, the activated myocardium close to the pacing site has been directly induced by pacing, and therefore depolarized to generate a resultant current source, which followed by the subsequent QRS complex, which is the apparent activation stage III.

Fig. 4. shows examples of comparison between the estimated results by the CDR/SMD methods and the recorded maps by the NCM system. In Fig. 4A, a pacing stimulation has been induced at the site of the LVL in pig #1. By applying the CDR/SMD inverse analysis on the collected BSPMs, the isopotential contour map and CDR map both have been estimated for the early QRS complex (0 ms - 20 ms corresponding to the captured beat in Fig. 3). The reconstructed isopotential map and CDR map at the QRS onset instant (20 ms after the pacing stimulation) are shown in the left panel and middle panel of Fig. 4A respectively. In the isopotential map, the isopotential contour lines with an increment of 0.05 mV are depicted with the 87 surface electrodes (one bad channel was excluded). The zero potential contour is indicated by a black curve, and the red lines and the blue lines depict the positive and negative isopotential contour area, respectively. The innermost red or blue contours indicate the positions of the maximum or minimum, specifically. The potential range for each potential isochrone is shown as the "P_Range" between the minimum and maximum value of the surface potential. As shown in the isopotential map, the body surface isopotential contour indicates a dipolar pattern of the projected cardiac activation on the left-anterior surface of the torso at the onset instant 20 ms after pacing on the LVL site. The inverse solutions of the CDR with the MNLS approach are shown as a CDR map for every sampling instant (see the middle panel of Fig. 4A for the onset instant). According to cardiac electrophysiology, the myocardium at the wavefront of depolarization corresponds to the cardiac current source with the highest amplitude of current density, while the rest non-depolarized myocardium corresponds to those areas showing less or no electrical activity. The distributed information about the extents of the activated areas is identified accordingly and shown as a color coded surface plot of the LV, where current densities are displayed for every patch of endocardial surface of the LV with a threshold set at 90% of the maximum dipole moment. As shown in the CDR map for the onset instant, the "hot spot" (yellow area) of the source activity is located on the higher left-anterior lateral area of the LV. This result agrees approximately with the view of the corresponding endocardial surface potential map exported from the invasive NCM system at 20 ms after pacing stimulation (mV, see the right panel of Fig. 4A), suggesting that the sources of the induced ectopic activity located around the pacing site for the early QRS complex. It is noteworthy that there is a little bit difference in the shape, area, and location of the "hot spot" between the estimated CDR map and recorded NCM map. The location of maximum point of the "hot spot" area is further

indicated in the CDR map by a white dipole labeled with “CDR_{max}”, and compared to the recorded position of the pacing site indicated by a green ball labeled with “PS”, as well as the corresponding optimal SMD indicated by a blue dipole labeled with “SMD”.

Similar analyses were performed in pigs #2, #3, and #4. Fig. 4B shows the results obtained in pig #2 at the onset instant 16 ms after pacing stimulation on the LVA site. In Fig. 4B, the “hot spot” of the source activity estimated by the CDR is located on the apical area of the LV that shows a good consistency with the direct mapping result by the NCM system. The upper-positive/lower-negative dipolar pattern observed from the surface potential map also provides a projected view of the inside ectopic activity due to the pacing at the apical area of the LV. As shown in Figs. 4C and 4D, reasonable results were also obtained in pig #3 and #4. Note that the views onto the isopotential maps in Figs. 4B, C, and D are observed from the anterior oblique view as indicated in the legend of those subfigure, in which all are different from the left-posterior oblique view of the heart of pig #1 paced from around the apex-anterior area, as shown in subfigure Fig. 4A.

Table 2 presents a summary of the quantitative evaluation of the CDR. The relative ability of the CDR (or SMD) method to localize the ectopic activity was assessed using the mean distances between the locations of the maximum CDR points (or the optimal SMD) and the precise pacing sites. For each pacing study, the locations of the “hot spots” of the source activities estimated on six well-captured beats varied. Using the procedure described in evaluation protocol, the localization accuracy of the CDR method in terms of $D_m \pm S_d$ was analyzed statistically, additionally refereed to the results using the SMD method that has been reported in our previous study. In total, 60 paced beats were analyzed (six for each site). At the onset of QRS (10 – 25 ms after the pacing spike), the averaged LEs of the source of ectopic activation were 16.9 ± 4.6 mm for the CDR approach (1 mm, the spatial resolution of the endocardial source distribution) and 18.4 ± 3.4 mm for the SMD method, respectively. In addition to the source location, the estimated mean distribution of the extents of activated sources was 20.1 ± 3.7 cm², and the potential distribution recorded by the NCM system was 19.2 ± 2.9 cm² over 60 ectopic beats. These results show that the “hot spot” estimated by the CDR method was closely related to that recorded by the NCM system either in their positions or areas, and the localization accuracy of the CDR technique was slightly better than that of the SMD method for the early QRS complex.

Discussion

Localization of source of cardiac ectopic activity has direct clinical benefits for determining the location of the corresponding ectopic focus. There have been numerous efforts to develop various imaging methods to localize and image cardiac electrical activity. Among those, a method on cardiac source imaging was reported in terms of two-dimensional endocardial surface current density reconstruction (Leder *et al* 1998a), and shown the potential in finding where the cardiac ectopic activity is from by analyzing the obtained clinical data (Leder *et al* 1998b, Nenonen *et al* 2001, Goernig *et al* 2009). Previously, some efforts have been made to assess the feasibility of the proposed CDR approach in cardiac source localization and arrhythmogenic myocardium identification, using either computer simulations or qualitative analysis with noninvasive BSPMs/MCGs in human. By means of the current density localization, Leder *et al* (2001a) calculated the pathway of atrio-ventricular pre-excitation with MCGs in a patient suffering from WPW syndrome. Their one-patient case report showed that the CDR solution in terms of the location of the highest current density has a good source localization ability at the early stage of the delta wave (15-35 ms) by comparing with the site of catheter ablation. Moreover, the estimated current density distribution in terms of a circumscribed source area with a higher current density on the endocardial surface could be useful to estimate the size of the suspected source region.

Furthermore, similar investigations of the endocardial surface CDR localization have been performed on the individual LV surface in patients suffering from previous MI (Leder *et al.* 2001b), coronary artery disease (CAD) (Leder *et al.* 1998a, b, Nenonen *et al.* 2001), and sustained VT (Leder *et al.* 2001b). At the same time, few studies were conducted on the quantitative assessment of performance of the endocardial surface CDR localization.

Rigorous validation of the CDR inverse results is important in source imaging due to the sophisticated nature of the CDR inverse problem and multiple factors involved in determining the accuracy of source localization, such as heart-torso conductor modeling, source modeling error, and measurement noise, etc. In the present study, we have experimentally evaluated the endocardial surface CDR approach regarding cardiac source localization, and to rigorously assess the accuracy and reliability of approximating cardiac electrical activity using the endocardial surface current density inverse solutions. Specifically, we chose the *in vivo* swine model in this study because of its close approximation to human cardiac size, heart-torso geometry, and electrophysiological characteristics. Furthermore, the simultaneous intracavitary mapping data recorded directly by a clinical NCM system during experiments provided supporting evidence for the localization of these PSs within the LV that generated the corresponding ectopic beats. As a result, the LE of the CDR localization in terms of the location of the highest current density was shown by the statistical analysis of the LEs in around 16.9 ± 4.6 mm. Compared to the well established non-invasive SMD localization method previously evaluated with a similar experimental protocol (LEs = 18.4 ± 3.4 mm, see Lai *et al.* 2010), the present experimental results with a lower average LEs indicate a bit better ability of CDR technique to localize endocardial ectopic sources induced by the endocardial pacing, although the SMD shows a lower or higher localization error compared to that of the CDR over the different pacing scenarios (see Table 2). The difference on the source space between the whole heart volume for the SMD and the endocardial surface of one ventricle for the CDR may contribute to the difference on the corresponding LEs. Additionally, compared with the other established localization methods with an inverse model either in the whole volume of the heart or on the epicardial/endocardial surface of the ventricles (Tilg *et al.* 2002, Zhang *et al.* 2005), the endocardial CDR approach validated in this study shows a relatively higher computational efficacy with a source model constraint applied only on the endocardium of the LV. Furthermore, the advantage of the present study are the use of an *in vivo* and intact large mammalian model, the simultaneous measurements of the non-invasive surface ECGs and the minimally-invasive intracavitary ECGs, and the near-clinical cardiac catheterization setting with a clinical NCM system, which provided a valuable consideration of the efficiency of the localization performance of the endocardial surface CDR technique for potential clinical applications. Currently, cardiac ablation techniques have been used in a growing number of patients with a variety of supraventricular and ventricular tachycardia. In this case, a non-invasive technique with an accuracy of ~20 mm may guide detailed endocardial mapping aiding catheter ablation. Thus, the non-invasive endocardial CDR localization approach could be useful in providing an alternative method for localizing the position of the origin of endocardial ectopic activity in patient, and may improve the clinical outcome of the current catheterization procedure.

It should be noted that the calculated current density distributions by the endocardial surface CDR method and the reconstructed endocardial potential maps by the NCM system vary from time to time, and the onset instant of the QRS complex has been determined manually, as shown in Fig. 5 and Fig. 6 for the example pacing on the LVL site in pig #1. Fig 5. shows the potential maps obtained by the NCM system and the estimated current density distribution by the CDR method, in which both results are unstable during the earlier activation of this beat, and then both results begin to continuously evolve from the pacing site to its surrounding areas from the instant 20 ms after pacing. In detail, the observed

activation was not apparent since only a small number of myocardial cells have been activated around the pacing site. After this period (20 ms after pacing, as shown in Fig. 5) of the propagation of cardiac activation, the beginning of an apparent activation could be observed clearly from the ECGs and the magnitude of the measured surface potentials is apparently larger than that of noise. Besides the qualitative illustration how the activation propagates during the earlier activation, this study has also employed an approximate measurement, the maximum point of the “hot spot” CDR (Muller *et al* 1999, Bai *et al* 2007), to quantitatively observe the CDR changes over time. The strength of maximum point of the “hot spot” has been calculated at each time instant during the early activation. As shown in Fig. 6, the strength was continually around $0 \mu\text{A}/\text{mm}^2$ before the onset instant (20 ms after pacing spike) and then gradually rose along the time. Thus, this time point ending of stage II is defined as the onset instant of the QRS complex that corresponds to the initiation of activation. It was the time instant of 20 ms after pacing spike for this pacing example in pig #1. Moreover, the onset instant of the QRS complex of each ectopic beat that corresponds to the initiation of the activation was manually determined at the time when the magnitude of the measured surface potentials is apparently larger than that of noise in this study.

Employing the simultaneous invasive endocardial mapping together with BSPMs recording represents a unique feature of the present study. Since the endocardial surface current density source model considers equivalent sources only on the endocardial surface of the LV, the simultaneous intracavitary mapping provides a desired means of assessing this CDR method. Nonetheless, the endocardial surface CDR approach may be limited in that it does not account for the three dimensional nature of cardiac electrical activity and the anisotropic nature of myocardium. Therefore, localization error might be introduced as well due to such simplification of the anisotropic myocardium in the BEM torso model, neglect of the intracavitary catheter in the inverse estimation, and neglect of the contribution of the three dimensional myocardial activation involving different myocardial layers even in the early activation stage. As described in Section II, in order to determine the endocardial pacing sites in the heart-torso model, the endocardial surface recorded by the NCM system was registered with the corresponding surface of the beating heart segmented from the preoperative MR images. Although both of the endocardial surfaces correspond to the end of diastole, they may not match exactly due to the complex positional and size changes that may occur during the cardiac and respiratory cycles. Because of this problem, errors might also be introduced when the registration procedure is applied. Moreover, the present study did not include any clinical abnormal ventricular activities, such as the WPW syndrome, malignant VT, and MI case, but a well controlled but simple pacing induced ectopic activity. The related clinical and mathematical studies on such actual arrhythmia cases would be expected to share a direct contribution to the clinical investigation (SippensGroenewegen *et al.* 1993, Muller *et al* 1999, Leder *et al* 2001b). It also would be valuable for the CDR method to further assess the localization error of the endocardial ectopic activity in humans compared to invasive methods (Berger *et al* 2006, Cuculich *et al* 2010). Additionally, the present study used the maximum point of the “hot spot” area to evaluation the performance of the CDR method. Thus, one should be cautious when using current density maps with multiple “hot spot” or patchy current density distributions to localize the initial site of such cardiac ectopic activity. Multiple regional maxima, the “hot spots”, may exist and thus increase the difficulty of determining the precise localization. Nonetheless the endocardial surface CDR approach provides a convenient and robust method of localizing and imaging cardiac activity of endocardial origin.

In summary, we revisited the CDR approach in a well-controlled experimental protocol in this study, and have conducted an experimental study in 4 pigs to evaluate the endocardial surface current density method for noninvasive localization of cardiac ectopic activity induced by endocardial pacing. The present results suggest that the endocardial surface

current density reconstruction could portray the origin and distribution of a cardiac ectopic activity during the early stage of ventricular depolarization, and have the potential to noninvasively estimate the anatomical origin of certain types of well-localized cardiac disorders of endocardial origin.

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Figure 1.

Illustration of an endocardial current density distribution which approximates the real three-dimensional current density distribution, when the cardiac source is of endocardial origin and the activation is at its earlier stage.

Figure 2.

Schematic diagram of electrocardiogram inverse solution and evaluation procedure. CDR represents the current density reconstruction method, SMD represents the signal moving dipole method, CDR_{max} represents the maximum point of in estimated current density map, IS_SMD represents the estimated 'initiation site' of the ectopic activity by the SMD, PS represents the 'pacing site' recorded by the intracavitary noncontact mapping (NCM) system, and CDR Map represents the estimated 'activation distribution' of the ectopic activity using the CDM method, in which the red dot indicates the location of pacing lead.

Figure 3.

A torso model with illustration of body surface electrode positions and the recorded surface ECGs in a butterfly format during pacing at the site of LVL, which is defined as three activation sub-stages: I. artificial spike stage; II. inapparent activation stage; III. apparent activation stage.

BSPM Recording **CDR/SMD Estimation** **NCM Mapping** **(A)****BSPM Recording** **CDR/SMD Estimation** **NCM Mapping** **(B)**

Figure 4.

Examples of the CDR localization. (a). Results in pig #1 at the onset of QRS complex following pacing at the site of LVL (20 ms after pacing spike), (b) Results in pig #2 at the onset of QRS complex following pacing at the site of LVA (16 ms after pacing spike), (c) Results in pig #3 at the onset of QRS complex following pacing at the site of LVAn (14 ms after pacing spike), and (d) Results in pig #4 at the onset of QRS complex following pacing at the site of LVAn (18 ms after pacing spike). The subfigures include the 'BSPM Recording' isopotential map, the 'CDR/SMD Estimation', and the 'NCM mapping' map. The view angle of each subfigure is represented by the image of human torso at lower right corner. Each isopotential map is depicted with effective surface electrodes by the increment of 0.05 mV. In each middle panel, the estimated current densities are displayed for every patch of the LV with a threshold set at 90% of the maximum dipole moment ($\mu\text{A}/\text{mm}^2$). And, each right panel shows the view of the corresponding potential map directly recorded by the invasive NCM system (mV).

Figure 5. Results in pig #1 during early ventricular depolarization following pacing at the site of LVL (at 2ms, 5ms, 10ms, 15ms, 20ms, and 22 ms after pacing spike). In subfigures: (a) the calculated source locations and extended distribution of ectopic beat and (b) the recorded pacing leads and potential maps.

Figure 6.

Results of localization of the initial site of cardiac ectopic activity by means of the CDR_{max} and SMD in pig #1 during early ventricular depolarization following pacing at the site of LVL (40 ms after pacing spike). In subfigures: (a) localization coordinates and current density of the maximum value point over the current density distribution and (b) localization coordinates and strength of the current dipole. CDR_{max} represents the calculated absolute current density value of each maximum point in the estimated current density map at each time instant. Str represents the calculated absolute strength value of the current dipole. LE represents CDR_{max} or SMD Localization Error, the mean distances (mm) over six beats between the location of the maximum current density point or the optimal SMD and the precise pacing site. X, Y, Z are corresponding to the axis X, Y, Z shown in Fig. 3, respectively, I, II, III are corresponding to the three sub-stages of early QRS complex of an ectopic beat, see detail in the Results section.

TABLE 1

Experimental and Modeling Parameters

Pig No.	Pacing sites	Surface electrodes	Torso model	Current sources
1	LVL, LVS, LVAn	88	5104	923
2	LVA, LVL, LVAn	90	6152	875
3	LVAn, LVS	85	5672	709
4	LVAn, LVL	83	6310	890

TABLE 2

Localization Errors and Averaged Current Density and Potential Distributions over Six Beats[†]

Fig No. / Pacing Site	CDR _{max} (μA/mm ²)	Localization Error (mm)		Source Distribution (cm ²)		QRS _{onset} (ms)
		CDR _{max}	SMD	CDR _{90%}	NCM _{90%}	
Fig 1-0806						
LVL	3.0 ± 1.3	10.8 ± 3.7	15.5 ± 4.4	20.2 ± 3.5	18.4 ± 3.9	20-25
LVS	5.3 ± 2.2	15.2 ± 1.4	13.1 ± 3.3	23.3 ± 3.1	24.4 ± 3.1	23-30
LVA _n	4.2 ± 0.8	23.5 ± 7.7	10.6 ± 2.6	21.1 ± 1.4	22.2 ± 2.2	14-22
Fig 2-0506						
LVA	4.0 ± 1.1	7.0 ± 4.4	27.8 ± 7.1	23.4 ± 2.0	20.2 ± 2.4	10-19
LVL	3.2 ± 1.2	17.1 ± 4.7	21.5 ± 3.5	25.3 ± 2.7	22.8 ± 1.5	11-14
LVA _n	8.6 ± 1.4	19.2 ± 7.9	13.1 ± 1.9	20.5 ± 1.2	19.2 ± 1.6	15-18
Fig 3-0716						
LVA _n	5.4 ± 2.2	9.6 ± 4.6	13.7 ± 2.0	18.8 ± 4.3	15.3 ± 2.0	10-15
LVS	6.4 ± 5.5	28.2 ± 1.2	24.5 ± 3.2	20.9 ± 6.2	17.9 ± 4.3	10-14
Fig 4-0303						
LVA _n	2.5 ± 1.5	12.5 ± 3.5	24.4 ± 3.3	14.2 ± 7.1	16.4 ± 5.2	15-23
LVA	1.9 ± 1.5	26.3 ± 6.8	19.6 ± 3.0	13.2 ± 5.1	15.1 ± 3.2	12-16

SMD, single move dipole; CDR, current density reconstruction; CDR_{max}, the maximum current density (μA/mm²) over the LV endocardial current sources; CDR_{max} or SMD Localization Error, the mean distances (mm) over six beats between the location of the maximum current density point or the optimal SMD and the precise pacing site; CDR_{90%} or NCM_{90%} source distributions, the mean areas (cm²) over six beats using a threshold set at 90% of the maximum current density or maximum potential; QRS_{onset}, the onset instant (ms) of the QRS complex after the pacing instant of 0 ms; LV, left ventricular.

Note: current density is defined as dipole moment per unit area along the endocardial surface area (unit: μA/mm²).

[†] Values are means ± SD.